History of Medicine, 2022, 8(2): 35–42
DOI: 10.17720/2409-5834.v8.1.2022.005

Assessment of Vitamin D Level as a Risk Factor and Illness Severity Indicator in COVID 19 Cases

Salma Mohamed Sabir[1], May Khalil Ismail[2*], Eman Hassan Ibrahim[3], Zahra Arshad Khan[4]

[1] *Post graduate Student, Medical Laboratory Sciences, College of Health Sciences, Gulf Medical University / UAE*
[2] *Associate professor, (Biochemistry), Department of Biomedical Sciences, College of Medicine, Gulf Medical University / UAE*
[3] *Assistant professor, (Pathology), Department of Biomedical Sciences, College of Medicine, Gulf Medical University / UAE*
[4] *Teaching Assistant, Department of Biomedical Sciences, College of Medicine, Gulf Medical University / UAE*

Corresponding author: May Khalil Ismail (dr.maykhalil@gmu.ac.ae)

Received: 15 May 2022 **Accepted:** 3 July 2022

Citation: Sabir SM, Ismail MK, Ibrahim EH, Khan ZA (2022) Assessment of Vitamin D Level as a Risk Factor and Illness Severity Indicator in COVID 19 Cases. History of Medicine 8(2): 35–42. https://doi.org/10.17720/2409-5834.v8.1.2022.005

Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-COV2) viruses using angiotensin-converting enzyme 2 (ACE2) receptors, to enter human cells, these receptors are highly expressed in the lung alveolar cells, vascular endothelium, cardiac myocytes, and other cells. Inadequate vitamin D levels in the blood have been linked to a higher risk of COVID-19 severity. **Objective:** To determine the association between Vitamin D level and severity of COVID-19 infection. **Materials and Method*:*** A cross sectional study was conducted at Thumbay Hospital, Ajman, UAE. Enrolled 70 COVID-19 positive hospitalized patients with age group ≥ 18 years old of both genders. Patients taking vitamin D supplements were excluded from the study. The biochemical analysis for the collected blood samples was performed on the automated analyzer and assessed for significance analysis. **Result:** There is a statistically significant correlation between Vitamin D levels and disease severity ($p < 0.05$) as determined by Pearson's Chi-square test. Independent t-test shown that there is a statistically significant difference with regards to gender, age groups, and co morbidity ($p < 0.05$). Pearson's correlation revealed a moderate, positive correlation between Vitamin D levels and the severity of COVID-19 infection, which was statistically significant. **Conclusion:** Vitamin D levels affect COVID-19 severity, with more severe cases showing vitamin D levels lower than normal when compared to severe cases with sufficient vitamin D levels. Furthermore, blood vitamin D levels are linked to age groups in COVID-19 patients. Vitamin D insufficiency and deficiency, on the other hand, was not linked to a higher risk of death prognosis, and co morbidities.

Keyword
COVID-19 infection, diseases severity, Vitamin D level, Co-morbidity

The global pandemic was declared a by the World Health Organization (WHO) on March 11, 2020, WHO nomenclature the epidemic disease outbreak of SARS-CoV-2 as Coronavirus disease 2019 (COVID-19) (Jain et al., 2020). The SARS-COV2 is single positive stranded enveloped RNA virus, to enter human cells uses the angiotensin-converting enzyme 2 (ACE2) receptors. These receptors are highly expressed in the lung alveolar cells, vascular endothelium, cardiac myocytes, and other cells (Al-Harbi et al., 2021). Various clinical manifestations with different severity are associated with COVID-19 infection, ranging from asymptomatic patients to pneumonia that develops into acute respiratory distress syndrome (ARDS) and multiple organ failure resulting in death. Elderly (>65 years old) and those with associated comorbidities, such as diabetes, hypertension, and chronic obstructive pulmonary disease, are more likely to suffer from severe illness (Somasundaram et al., 2020).

Vitamin D is a fat-soluble known as steroid prohormone with endocrine, paracrine, and autocrine

functions that plays an essential role as a prohormone that maintains bone homeostasis and mediates many essential non-skeletal functions (AlSafar et al., 2021). Several studies have shown that Vitamin D plays a role in regulating innate and adaptive immune responses, promoting antiviral effector mechanisms, and reducing the expression of several pro-inflammatory cytokines(Infante et al., 2022). Vitamin D partly enhances cellular innate immunity by inducing antimicrobial peptides, including human Cathelicidin and defensins. Cathelicidin exhibits direct antimicrobial activities against a spectrum of microbes, including Gram-positive and Gram-negative bacteria, enveloped and nonenveloped viruses and fungi (Grant et al., 2020). Several lines of evidence might support a role for vitamin D status in SARS COV-2 infection. Patients with severe manifestations of COVID-19 exhibit significantly increased circulating levels of several pro-inflammatory cytokines and chemokines, these abnormal immune responses can lead to acute respiratory distress syndrome, and multiorgan failure (Ghelani, Alesi, & Mousa, 2021).

The severity of disease has been found to be highly correlated with age. Children are less frequently and less severely affected than adults and geriatrics (Dong et al., 2020). In the reported literature, COVID-19 infection is also strongly associated with pre-existing comorbidities such as hypertension, diabetes, obesity, chronic obstructive pulmonary disease, cardiovascular disease, malignancy, HIV, and kidney disease, which increase the risk of infection and severity of disease and mortality (Ben-Eltriki et al., 2022; Sanyaolu et al., 2020).

Vitamin D deficiency is a public health concern, and some evidence links low serum vitamin D levels to acute respiratory tract infections (Greiller & Martineau, 2015). COVID-19 severity has been linked to low vitamin D levels in the blood, despite the vaccine deployment and positive initial results, the focus of COVID-19 management remains on further preventative measures.

Methods

A cross sectional study was conducted at Thumbay Hospital and Thumbay Labs, Gulf Medical University (GMU), Ajman, United Arab Emirates (UAE). Ethical approval was obtained from the Ethics and Research committees (IRB) of Gulf Medical University (April 2021). Data collection was done between March-August 2021.

Total of 70 patients with confirmed diagnosis of COVID-19 aged ≥ 18 years with the consent to participate in the study were recruited and written consent forms were obtained from all subjects.

Patients with COVID-19 taking vitamin D supplementation & less than 18 years old were excluded from the study.

A fully automated analyzer (Beckman Coulter UniCel DxI 800 Analyzer) was used to determine Vitamin D levels in the serum of COVID-19 patients. The instrument was validated as per the recommended validatory procedure. Whole blood samples (3-5 ml) were collected from the COVID-19 positive patients. The Access 25(OH) Vitamin D total assay is a two-step competitive binding immunoenzymatically assay. In the initial incubation, sample is added to a reaction vessel with a DBP (vitamin D binding protein) releasing agent and paramagnetic particles coated with sheep monoclonal anti-25(OH) Vitamin D antibody. A 25(OH) Vitamin D is released from DBP and binds to the immobilized monoclonal anti-25(OH) Vitamin D on the solid phase. Subsequently, a 25(OH) Vitamin D analogue-alkaline phosphatase conjugate is added which competes for binding to the immobilized monoclonal anti-25(OH) Vitamin D. After a second incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. The chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is inversely proportional to the concentration of 25(OH) Vitamin D in the sample.

The data was analyzed using the Statistical Package for Social Science (SPSS), version 26.0 software. Both descriptive and inferential statistics were used to describe the sample, identify differences in vitamin D level among groups. Descriptive statistics was used to describe patients' demographical characteristics represented as the mean ± standard deviation (SD). Independent T-tests were used for categorical and continuous variables to test the mean difference between the two study groups. Pearson's correlation used to find a linear relationship between the two continuous variables. While chi square used to find the association between categorical variables.

Results

The present study consisted of 70 patients with COVID-19 infection. The vast majority were male patients with a count of 55 cases (78.6 %) whereas female patients were reported to be 15 cases (21.4%).

There is a significant correlation between vitamin D

levels and the severity of positive COVID-19 patients (*p* value is 0.028). Most of mild, moderate, and severe cases (82%, 67% & 52% respectively) showed low vitamin D levels (Table 1).

Table 1: Association between Vitamin D levels and severity of COVID-19 infection.

Vitamin D Levels	Severity of COVID-19			Total	Pearson's X^2 *p* value
	Mild	Moderate	Severe		
Deficient	16 (44%)	15 (42%)	5 (14%)	36 (51.4%)	**0.028**
Insufficient	6 (38%)	4 (25%)	6 (38%)	16 (22.9%)	
Sufficient	2 (11%)	7 (39%)	9 (50%)	18 (25.7%)	
Total	24 (34%)	26 (37%)	20 (29%)	70 (100%)	

**P value < 0.05 is considered statistically significant.*

Statistically significant results (p value is 0.014) were found on analyzing vitamin D levels against admission of patients to Intensive Care Unit (ICU) as shown in (Table2).

Table 2: Association analysis between vitamin D levels and admission of patients to the ICU facility

Vitamin D Levels	ICU Admissions		Total	Pearson's X^2 *p* value
	Admitted	Not admitted		
Deficient	5 (13.9%)	31 (86.1%)	36 (51.4%)	**0.014**
Insufficient	6 (37.5%)	10 (62.5%)	16 (22.9%)	
Sufficient	9 (50%)	9 (50%)	18 (25.7%)	
Total	20 (28.6%)	50 (71.40%)	70 (100%)	

**P value < 0.05 is considered statistically significant*

On correlating the association between Vitamin D level and co morbidities, there is insignificant correlation between Vitamin D level and co morbidity (*p* value is 0.696) as 51.4% of cases showed no co morbidity, as in (Table 3).

Table 3: Association between Vitamin D levels and Co morbidity factors.

Vitamin D Levels	Co Morbidity					Total	Pearson's X^2 *p* value
	No co morbidities	Diabetes	Hypertension	Diabetes & Hypertension	COPD		
Deficient	21 (58.3%)	4 (11.1%)	2 (5.6%)	6 (16.7%)	3 (8.3%)	36 (51.4%)	0.696
Insufficient	8 (50%)	1 (6.3%)	2 (12.5%)	2 (12.5%)	3 (18.8%)	16 (22.9%)	
Sufficient	7(38.9%)	1 (5.6%)	2 (11.1%)	6 (33.3%)	2 (11.1%)	18 (25.6%)	
Total	36 (51.4%)	6 (8.6%)	6 (8.6%)	14 (20%)	8 (11.4%)	70 (100%)	

**P value < 0.05 is considered statistically significant*

The study findings shown that there is a significant correlation between the severity of disease and Co morbidity (*p* value is 0.008) and most of severe cases (40%) having combined diabetes & hypertension (Table 4).

Table 4: Association between Severity of COVID-19 and Co morbidity factors.

Severity of COVID-19	Co Morbidity					Total	Pearson's X^2 *p* value
	No co morbidities	Diabetes	Hypertension	Diabetes & Hypertension	COPD		
Mild	18 (75%)	1 (4.2%)	3 (12.5%)	0	2 (8.3%)	24 (34.3%)	**0.008**
Moderate	12 (46.2%)	1 (3.8%)	3 (11.5%)	6 (23.1%)	4 (15.4%)	26 (37.1%)	
Severe	6 (30%)	4 (20%)	0	8 (40%)	2 (10%)	20 (28.6%)	
TOTAL	36 (51.4%)	6 (8.6%)	6 (8.6%)	14 (20%)	8 (11.4%)	70 (100%)	

**P value < 0.05 is considered to be statistically significant*

The significance analysis of the gender across vitamin D levels with respect to the age group was also assessed to establish an understanding of these in the study population (Table 5).

Table 5: Association analysis between age groups and vitamin D levels with gender of the patients

Gender	Vitamin D Levels	Age group		Total	X^2 *p* value	
		<40	40>			
Male	Low	34 (85%)	6 (15%)	40 (72.7%)	**0.046**	**0.006**
	Adequate	9 (60%)	6 (40%)	15 (27.3%)		
	Total	43 (78.2%)	12 (21.8%)	55 (100%)		
Female	Low	11 (91.7%)	1 (8.3%)	12 (80%)	**0.024**	
	Adequate	1 (33.3%)	2 (66.75)	3 (20%)		
	Total	12 (80%)	3 (20%)	15 (100%)		

The present study finding shown that there is a significant correlation between the severity level of disease and age group (*p* value is 0.006) with respect to gender of the patients (Table 6)

Table 6: Association analysis between age groups and COVID-19 Severity levels with gender of the patients

Gender	COVID-19 Severity	Age group			Total	Pearson's X^2 p value	
		20-39	40-59	60<			
Male	Mild	8 (50%)	8 (50%)	0	16 (29.1%)	**0.046**	**0.**006
	Moderate	7 (31.8%)	**12 (54.5%)**	3 (13.6%)	22 (40%)		
	Severe	2 (11.8%)	6 (35.3%)	**9 (52.9%)**	17 (30.9%)		
Total		17 (30.9%)	26 (47.3%)	12 (21.8%)	**55 (100%)**		
Female	Mild	3 (37.5%)	**5 (62.5%)**	0	8 (53.3%)	**0.024**	
	Moderate	1 (25%)	1 (25%)	**2 (50%)**	4 (26.7%)		
	Severe	0	**2 (66.7%)**	1 (33.3%)	3 (20%)		
Total		4 (26.7%)	8 (53.3%)	3 (20%)	**15 (100%)**		

**P value < 0.05 is considered to be statistically significant*

Discussion

The main goal of the current study was to investigate the relationship between vitamin D level and COVID-19 severity and co morbidity. The present study found that there was a significant relationship between vitamin D level and COVID-19 severity. Moreover, there was a significant relationship in terms of COVID-19 severity level with co morbidity.

Affected individuals may be asymptomatic or develop mild, moderate, or severe illness, which can be deadly, depending on the degree of the illness. So far, older age, male sex, obesity, cardiovascular disease, chronic lung disease, diabetes mellitus, and cancer have been identified as particular risk factors for a serious illness. Because many of these risk variables are not modifiable, it is important to find modifiable factors that may contribute to the severity of COVID-19 infection. Diet and nutrition, particularly vitamin D levels, have a significant impact on immunological function and infection risk (Childs, Calder, & Miles, 2019). One possible controllable risk factor proposed to modify COVID-19 infection severity is vitamin D (Rhodes et al., 2021). Meltzer et al stated that vitamin D may influence immunological modulation in addition to its impact in bone health (Meltzer et al., 2020). Vitamin D receptors may be found in monocytes, activated T and B lymphocytes, and dendritic cells, which all play a role in immune control. Vitamin D has been demonstrated to influence cytokine production, lymphocyte proliferation, antibody formation, monocyte activation, and cell-mediated immunity (Meltzer et al., 2020).

Katz, Yue, and Xue (2021) & Meltzer et al. (2020) reported that vitamin D deficiency/insufficiency increases the risk of COVID-19 infection, which is consistent with our result as most of mild, moderate, and severe cases (82%, 67%, & 52% respectively) showed low vitamin D level. On the other hand, some studies have found no significant association between vitamin D level and COVID-19 infection severity (Cereda et al., 2021; De Smet et al., 2021; Hastie et al., 2020).

The present study revealed that the severity of COVID-19 was shown to be impacted by vitamin D levels, with most severe cases having vitamin D deficiency compared to mild and moderate cases having Vitamin D sufficiency and insufficiency ($p > 0.05$). Our findings agree with Wang et al who reported that there was a link between vitamin D deficiency and COVID19 infection severity, with greater rates of hospital admissions and longer hospital stays (Wang et al., 2022). This occurrence is thought to be related to vitamin D's immunomodulatory effect.

Vitamin D may have some of these effects by lowering the 'cytokine storm,' which has been linked to severe COVID19 infection, by modifying proinflammatory cytokine profiles, vitamin D reduces the formation of immune cells and slows the progression of the inflammatory cascade (Bilezikian et al., 2020). Calcitriol, a vitamin D active metabolite, has been found to suppress the production of proinflammatory cytokines such gamma interferon, tumor necrosis factor alpha, and IL- 2.(Wang et al., 2022). Another research verified the same findings, revealing that many COVID-19 patients admitted to hospitals had significant inflammation and low nutritional status, including vitamin D insufficiency. Furthermore, a considerable majority of patients develop respiratory failure within a few days, necessitating non-invasive ventilation or continuous positive airway pressure (Murdaca, Pioggia, & Negrini, 2020).

The damaged pulmonary endothelium caused by COVID19 entering through ACE2 receptors causes endothelial dysfunction, which interferes with the binding of insufficient vitamin D to its receptor, leading to additional inflammatory development and a higher risk of severity in COVID-19 (Zhang, McCullough, & Tecson, 2020).

The effect of high vitamin D levels in respiratory infections has been studied in several observational epidemiology studies and randomized controlled trials. According to a recent study, supplementing with vitamin D could help lessen the likelihood and severity of COVID-19 (Alipio, 2020). A recent randomized, double-blind, placebo-controlled clinical research found that vitamin D did not reduce hospital length of stay or disease severity (Taha et al., 2021).

There is a significant correlation between Vitamin D levels with age & gender of patient (p value is 0.006). Among males, 61.8% were below 40 years old and showed low Vitamin D level while 73.3% of female were below 40 years old and showed low Vitamin D level.

The current study found that no correlation between nationality and vitamin D levels. On contrast, Escobar et al. found that race is a significant influence, since multiple studies have indicated that in the United Kingdom and the United States, Black, Hispanic, and Asian people accounted for a disproportionately greater number of hospitalizations and fatalities related to COVID19 (Escobar et al., 2021).

In our study there is a significant correlation between the severity of disease and Co morbidity (*p* value is 0.008) and most of severe cases (40%) having combined diabetes & hypertension. These findings are consistent with Li et al who found that diabetes was two times more common in severe cases than in mild cases, and that 9.7% of COVID-19 patients had diabetes (Liang et al., 2020). Our findings are also in agreement with Emami et al. (2020) who reported that 85.4 % of severe COVID-19 patients had diabetes or cardiovascular disease.

According to Chinese research, Guan et al. (2020) showed the prevalence of diabetes in patients with severe COVID-19 ranges from 15% to 25%, which is two to four times greater than in non-critical patients. Furthermore, Parveen et al. (2020) reported that hypertension was the most common comorbidity among COVID-19 patients. It was estimated to have a prevalence of 17%, with severe cases having a two-fold greater frequency than mild cases (Parveen et al., 2020).

The higher percentage (73.3%) of female with low vitamin D level may be due to a smaller number of female cases. The present study shows a statistically significant correlation between gender, age, and severity of the disease. Among male mild, moderate and severe infection representing 29.1%, 40% & 30.9% respectively, on the other hand most of female cases (53.3%) were mild infection while moderate and severe infection representing 26.7% & 20% respectively. Most of severe cases (88.2% in male and 100% in female) were 40 years old and above. Our results are consistent with Raimondi et al. (2021) who stated that female patients have less severe illness and are more likely to survive the infection and with Mehra et al. (2020) who reported that males have a worse disease, according to epidemiological research.

The current study reveals that there is a statistically significant correlation (*p* value is 0.014) between vitamin D levels and admission of patients to ICU as those subjects, having low vitamin D levels were representing 15.7% (11 cases), on the other hand 12.9% (9 cases) of patients were admitted to ICU and having sufficient vitamin D level. Our results are in line with Charoenngam et al. (2021), who stated that lower vitamin D levels were typically connected with the risk of COVID-19 infection, admitting patients to ICU, the severity and prognosis and even dying from it, according to data from retrospective studies done in the United States and Europe (Charoenngam et al., 2021). Furthermore, our results are also in accordance with Braun et al. (2011) & de Haan et al. (2014) who said that vitamin D insufficiency is common among critically ill patients, and it has the potential to worsen their clinical outcomes by raising infection rates and death. Many observational studies have found a

strong link between vitamin D level and COVID-19 patients' likelihood of disease severity. Vitamin D insufficiency was linked to a greater risk of severe infection and ICU hospitalization in patients with COVID-19, according to a meta-analysis of 27 studies (Kazemi et al., 2021).

Considering the link between vitamin D levels in the blood and patient outcomes. The current investigation found that vitamin D levels had no effect on patient outcomes ($p > 0.05$). Bassatne et al. (2021) agreed to a similar result, reporting a statistically insignificant association between blood Vitamin D levels and mortality risk. On the other hand, our results are inconsistent with Wang et al. (2022) who said that in adult COVID19 patients, vitamin D insufficiency was linked to increased mortality, higher rates of hospital admissions, and longer hospital stays, according to a comprehensive analysis. Vitamin D's immunomodulatory effects, according to the study, may be achieved in part by vitamin D lowering the 'cytokine storm,' which has been linked to severe COVID19 infection (Wang et al., 2022). In addition, a recent comprehensive study done by Li and Ding (2020) reported that vitamin D insufficiency may increase mortality rates in patients with sepsis.

Conclusion

The current study found that vitamin D levels affect COVID-19 severity, with severe cases showing vitamin D insufficiency when compared to mild and moderate instances. Vitamin D insufficiency, on the other hand, was not linked to a higher risk of death prognosis.

Acknowledgments

We would like to express our gratitude to the management in Thumbay Ajman Hospital for the help and support that facilitate conducting this research. Our deep thanks to all COVID-19 patients who willingly participated in this study and made this research possible.

References

Al-Harbi S, Al-Harbi YA, Ezzat Abdellatif A, Al-Ahmadey ZZ, & Alahmadi S (2021) Retrospective evaluation of the serum level of vitamin D among COVID-19 patients in Al Madinah, Saudi Arabia. Biotechnol Biochem Res 9 (1): 8-13. DOI: https://doi.org/10.30918/BBR.91.21.018

Alipio M (2020) Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (COVID-19). SSRN Electronic Journal. DOI: http://dx.doi.org/10.2139/ssrn.3571484

AlSafar H, Grant WB, Hijazi R, Uddin M, Alkaabi N et al. (2021) COVID-19 disease severity and death in relation to vitamin D status among SARS-CoV-2-positive UAE residents. Nutrients 13 (5): 1714. DOI: https://doi.org/10.3390/nu13051714

Bassatne A, Basbous M, Chakhtoura M, El Zein O, Rahme M et al. (2021) The link between COVID-19 and VItamin D (VIVID): A systematic review and meta-analysis. Metabolism 119: 154753. DOI: https://doi.org/10.1016/j.metabol.2021.154753

Ben-Eltriki M, Hopefl R, Wright JM, & Deb S (2022) Association between vitamin D status and risk of developing severe COVID-19 infection: a meta-analysis of observational studies. Journal of the American Nutrition Association 41 (7): 679-689. DOI: https://doi.org/10.1080/07315724.2021.1951891

Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM et al. (2020) Mechanisms in endocrinology: vitamin D and COVID-19. European journal of endocrinology 183 (5): R133-R147. DOI: https://doi.org/10.1530/EJE-20-0665

Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y et al. (2011) Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Critical care medicine 39 (4): 671–677. DOI: https://doi.org/10.1097/CCM.0b013e318206ccdf

Cereda E, Bogliolo L, Klersy C, Lobascio F, Masi S et al. (2021) Vitamin D 25OH deficiency in COVID-19 patients admitted to a tertiary referral hospital. Clinical nutrition 40 (4): 2469-2472. DOI: https://doi.org/10.1016/j.clnu.2020.10.055

Charoenngam N, Shirvani A, Reddy N, Vodopivec DM, Apovian CM et al. (2021) Association of vitamin D status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. Endocrine Practice 27 (4): 271-278. DOI: https://doi.org/10.1016/j.eprac.2021.02.013

Childs CE, Calder PC, & Miles EA (2019) Diet and immune function. Nutrients 11 (8): 1933. DOI: https://doi.org/10.3390/nu11081933

de Haan K, Groeneveld A, de Geus HR, Egal M, & Struijs A (2014) Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Critical care 18 (6): 1-8. DOI: https://doi.org/10.1186/s13054-014-0660-4

De Smet D, De Smet K, Herroelen P, Gryspeerdt S, & Martens GA (2021) Serum 25 (OH) D level on hospital admission associated with COVID-19 stage and mortality. American journal of clinical pathology 155 (3): 381-388. DOI: https://doi.org/10.1093/ajcp/aqaa252

Dong Y, Mo X, Hu Y, Qi X, Jiang F et al. (2020) Epidemiology of COVID-19 among children in China. Pediatrics 145 (6): e20200702. DOI: https://doi.org/10.1542/peds.2020-0702

Emami A, Javanmardi F, Pirbonyeh N, & Akbari A (2020) Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Archives of academic emergency medicine 8 (1): e35. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096724

Escobar GJ, Adams AS, Liu VX, Soltesz L, Chen Y-FI et al. (2021) Racial disparities in COVID-19 testing and outcomes: retrospective cohort study in an integrated health system. Annals of internal medicine 174 (6): 786-793. DOI: https://doi.org/10.7326/M20-6979

Ghelani D, Alesi S, & Mousa A (2021) Vitamin D and COVID-19: An overview of recent evidence. International Journal of Molecular Sciences 22 (19): 10559. DOI: https://doi.org/10.3390/ijms221910559

Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB et al. (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12 (4): 988. DOI: https://doi.org/10.3390/nu12040988

Greiller CL, & Martineau AR (2015) Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 7 (6): 4240-4270. DOI: https://doi.org/10.3390/nu7064240

Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q et al. (2020) Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine 382 (18): 1708-1720. DOI: https://doi.org/10.1056/NEJMoa2002032

Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV et al. (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (4): 561-565. DOI: https://doi.org/10.1016/j.dsx.2020.04.050

Infante M, Buoso A, Pieri M, Lupisella S, Nuccetelli M et al. (2022) Low vitamin D status at admission as a risk factor for poor survival in hospitalized patients with COVID-19: an Italian retrospective study. Journal of the American Nutrition Association 41 (3): 250-265. DOI: https://doi.org/10.1080/07315724.2021.1877580

Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S et al. (2020) Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Scientific reports 10 (1): 20191. DOI: https://doi.org/10.1038/s41598-020-77093-z

Katz J, Yue S, & Xue W (2021) Increased risk for COVID-19 in patients with vitamin D deficiency. Nutrition 84: 111106. DOI: https://doi.org/10.1016/j.nut.2020.111106

Kazemi A, Mohammadi V, Aghababaee SK, Golzarand M, Clark CC et al. (2021) Association of vitamin D status with SARS-CoV-2 infection or COVID-19 severity: a systematic review and meta-analysis. Advances in Nutrition 12 (5): 1636-1658. DOI: https://doi.org/10.1093/advances/nmab012

Li Y, & Ding S (2020) Serum 25-Hydroxyvitamin D and the risk of mortality in adult patients with Sepsis: A meta-analysis. BMC infectious diseases 20 (1): 1-10. DOI: https://doi.org/10.1186/s12879-020-4879-1

Liang JJ, Liu J, Chen Y, Ye B, Li N et al. (2020) Characteristics of laboratory findings of COVID-19 patients with comorbid diabetes mellitus. Diabetes research and clinical practice 167: 108351. DOI: https://doi.org/10.1016/j.diabres.2020.108351

Mehra MR, Desai SS, Kuy S, Henry TD, & Patel AN (2020) Cardiovascular disease, drug therapy, and mortality in Covid-19. New England Journal of Medicine 382 (25): e102. DOI: https://do.org/10.1056/NEJMoa2007621

Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V et al. (2020) Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA network open 3 (9): e2019722. DOI: https://doi.org/10.1001/jamanetworkopen.2020.19722

Murdaca G, Pioggia G, & Negrini S (2020) Vitamin D and Covid-19: an update on evidence and potential therapeutic implications. Clinical and Molecular Allergy 18: 1-8. DOI: https://doi.org/10.1186/s12948-020-00139-0

Parveen R, Sehar N, Bajpai R, & Agarwal NB (2020) Association of diabetes and hypertension with disease severity in covid-19 patients: A systematic literature review and exploratory meta-analysis. Diabetes research and clinical practice 166: 108295. DOI: https://doi.org/10.1016/j.diabres.2020.108295

Raimondi F, Novelli L, Ghirardi A, Russo FM, Pellegrini D et al. (2021) Covid-19 and gender: lower rate but same mortality of severe disease in women—an observational study. BMC pulmonary medicine 21 (1): 1-11. DOI: https://doi.org/10.1186/s12890-021-01455-0

Rhodes JM, Subramanian S, Laird E, Griffin G, & Kenny RA (2021) Perspective: Vitamin D deficiency and COVID-19 severity–plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. Journal of internal medicine 289 (1): 97-115. DOI: https://doi.org/10.1111/joim.13149

Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K et al. (2020) Comorbidity and its impact on patients with COVID-19. SN comprehensive clinical medicine 2: 1069-1076. DOI: https://doi.org/10.1007/s42399-020-00363-4

Somasundaram NP, Ranathunga I, Ratnasamy V, Wijewickrama PSA, Dissanayake HA et al. (2020) The impact of SARS-Cov-2 virus infection on the endocrine system. Journal of the Endocrine Society 4 (8): bvaa082. DOI: https://doi.org/10.1210/jendso/bvaa082

Taha R, Abureesh S, Alghamdi S, Hassan RY, Cheikh MM et al. (2021) The relationship between vitamin D and infections including COVID-19: any hopes? International journal of general medicine: 3849-3870. URL: https://www.tandfonline.com/doi/full/10.2147/IJGM.S317421

Wang Z, Joshi A, Leopold K, Jackson S, Christensen S et al. (2022) Association of vitamin D deficiency with COVID-19 infection severity: Systematic review and meta-analysis. Clinical Endocrinology 96 (3): 281-287. DOI: https://doi.org/10.1111/cen.14540

Zhang J, McCullough PA, & Tecson KM (2020) Vitamin D deficiency in association with endothelial dysfunction: Implications for patients withCOVID-19. Reviews in cardiovascular medicine 21 (3): 339-344. DOI: https://doi.org/10.31083/j.rcm.2020.03.131